Human endothelial reprogramming for hematopoietic stem cell therapy.

Grant Award Details

Human endothelial reprogramming for hematopoietic stem cell therapy.

Grant Type: New Faculty Physician Scientist

Grant Number: RN3-06479

Project Objective: To engineer mature human hemogenic endothelium for in vitro production of hematopoietic stem cells.

Investigator:

Name:	Ann Zovein
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Blood Disorders, Blood Cancer, Cancer

Human Stem Cell Use: iPS Cell, Directly Reprogrammed Cell

Cell Line Generation: Directly Reprogrammed Cell

Award Value: $2,319,784

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Human endothelial reprogramming for hematopoietic stem cell therapy.

Public Abstract: The current roadblocks to hematopoietic stem cell (HSC) therapies include the rarity of matched donors for bone marrow transplant, engraftment failures, common shortages of donated blood, and the inability to expand HSCs ex vivo in large numbers. These major obstacles would cease to exist if an extensive, bankable, inexhaustible, and patient-matched supply of blood were available. The recent validation of hemogenic endothelium (blood vessel cells lining the vessel wall give rise to blood stem cells) has introduced new possibilities in hematopoietic stem cell therapy. As the phenomenon of hemogenic endothelium only occurs during embryonic development, we aim to understand the requirements for the process and to re-engineer mature human endothelium (blood vessels) into once again producing blood stem cells (HSCs). The approach of re-engineering tissue specific de-differentiation will accelerate the pace of discovery and translation to human disease. Engineering endothelium into large-scale hematopoietic factories can provide substantial numbers of pure hematopoietic stem cells for clinical use. Higher numbers of cells, and the ability to grow cells from matched donors (or the patients themselves) will increase engraftment and decrease rejection of bone marrow transplantation. In addition, the ability to program mature lineage restricted cells into more primitive versions of the same cell lineage will capitalize on cell renewal properties while minimizing malignancy risk.

Statement of Benefit to California: Bone marrow transplantation saves the lives of millions with leukemia and other diseases including genetic or immunologic blood disorders. California has over 15 centers serving the population for bone marrow transplantation. While bone marrow transplantation can be seen as a standard to which all stem cell therapies should aspire, there still remains the difficulty of finding matched donors, complications such as graft versus host disease, and the recurrence of malignancy. While cord blood has provided another donor source of stem cells and improved engraftment, it still requires pooling from multiple donors for sufficient cell numbers to be transplanted, which may increase transplant risk. By understanding how to reprogram blood vessels (such as those in the umbilical cord) for production of blood stem cells (as it once did during human development), it could eventually be possible to bank umbilical cord vessels to provide a patient matched reproducible supply of pure blood stem cells for the entire life of the patient. Higher numbers of cells, and the ability to grow cells from matched donors (or the patients themselves) will increase engraftment and decrease rejection of bone marrow transplantation. In addition, the proposed work will introduce a new approach to engineering human cells. The ability to turn back the clock to near mature cell specific stages without going all the way back to early embryonic stem cell stages will reduce the risk of malignancy.